2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of boron and compounds and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for boron based on toxicologicalstudies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-- inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate(15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposureassociated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the

application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans or animals after inhalation exposure to boron.

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, or renal effects in humans after inhalation exposure to boron. No studies were located regarding dermal/ocular effects after acute inhalation exposure in humans or animals for any duration category.

Information on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, renal, and dermal/ocular effects is discussed below. The highest NOAEL values and all reliable LOAEL values for these systemic effects for each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

Respiratory Effects. Boron (as boron oxide and boric acid dusts) has been shown to cause irritation of the upper respiratory tract in humans. Based on a medical questionnaire from 113 workers (96% males, 4% females) employed in the borax industry for an average of 11 years, mean exposures of 4.1 mg/m^3 to boron oxide and boric acid dusts were associated with dryness of the mouth, nose, or throat, sore throat, and productive cough (Garabrant et al. 1984). While the authors reported differences between the test and control groups in age and numbers of smokers, no differences in symptoms were observed. Similarly, symptoms of acute respiratory irritation were related to exposures to borax dust at concentrations of 4 mg/m^3 or more in a crosssectional study of 629 borax workers actively employed for 11.4 years (Garabrant et al. 1985). Decreases in the forced expiratory volume (FEV_1) were seen among smokers who had cumulative borax exposures of 80 mg/m^3 or greater but were not seen among less exposed smokers or among nonsmokers. Radiographic abnormalities were not found. It was determined in a follow-up of the Garabrant et al. 1985 study that the cumulative borax exposure effect

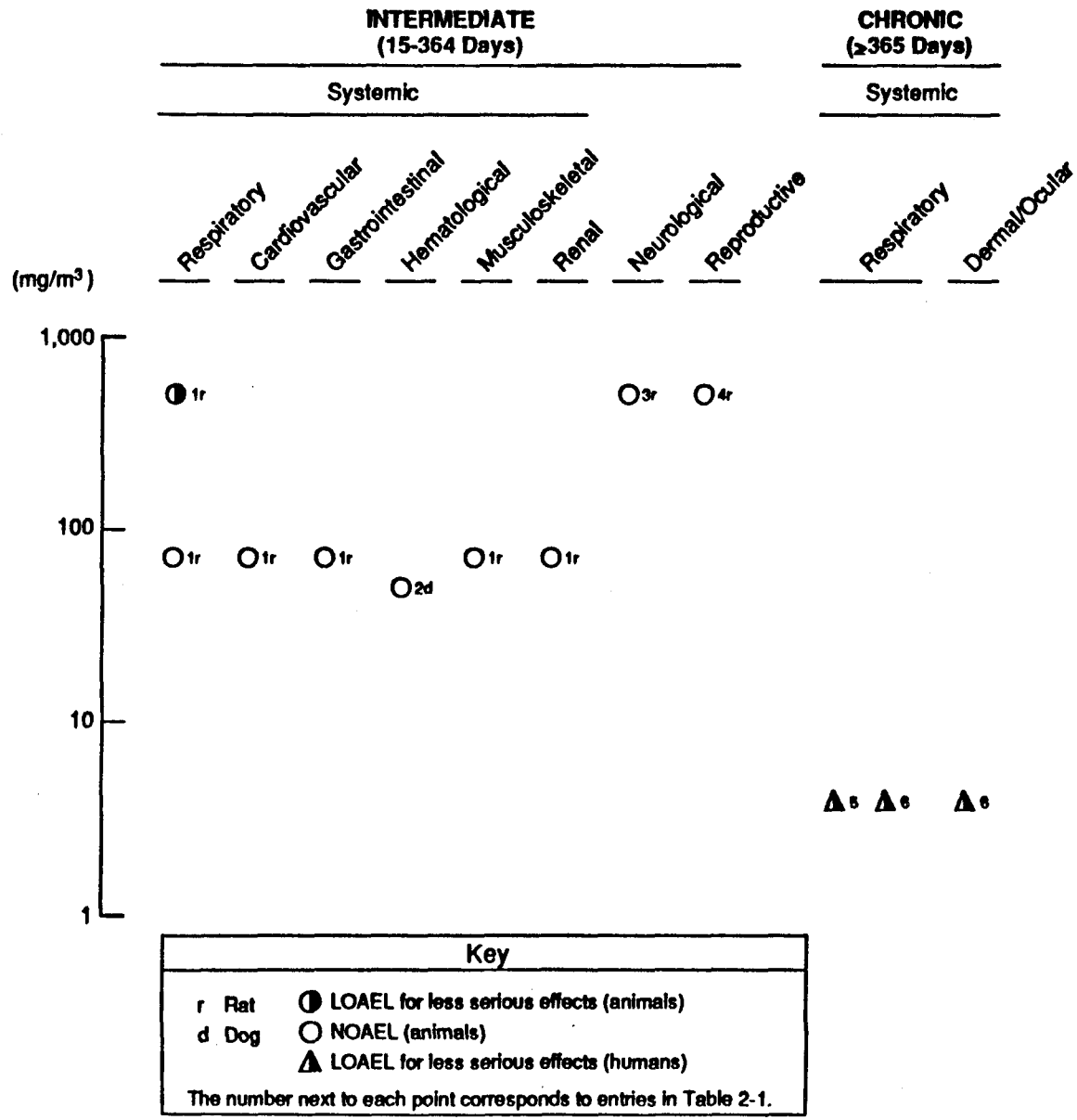
TABLE 2-1. Levels of Significant Exposure to Boron and Compounds - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference	Form
INTERMEDIATE EXPOSURE								
Systemic								
1	Rat	6-24 wk 5d/wk 6hr/d	Resp	77	470 (respirtory irritation)		Wilding et al. 1959	BO
			Cardio	77				
			Musc/skel	77				
			Renal	77				
			Gastro	77				
2	Dog	23 wk	Hemato	57			Wilding et al. 1959	BO
Neurological								
3	Rat	6-24 wk 5d/wk 6hr/d		470			Wilding et al. 1959	BO
Reproductive								
4	Rat	6-24 wk 5d/wk 6hr/d		470			Wilding et al. 1959	BO
CHRONIC EXPOSURE								
Systemic								
5	Human	11.4 yr (mean)	Resp		4.1 (respiratory irritation)		Garabrant et al. 1985	BX
6	Human	11.4 yr (mean)	Resp		4.1 (respiratory irritation)		Garabrant et al. 1984	BX, BA, BO
			Derm/oc		4.1 (eye irritation)			

[a]The number corresponds to entries in Figure 2-1.

BA = boric acid; BO = boron oxide; BX = borax; Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); yr = year(s)

FIGURE 2-1. Levels of Significant Exposure to Boron and Compounds – Inhalation



found previously was probably due to smoking workers with longer boron work histories and who smoke disproportionately more than those with shorter work histories. There was no indication that borax exposure at the levels studied (up to 15 mg/m^3) impaired pulmonary function (Wegman et al. 1991). Direct irritation to mucous membranes of the nose and throat was also studied by Wegman et al. (1991) using an irritation scoring system together with realtime measurements of borax exposure concentrations. The study concluded that borates 'are mild irritants. However, these effects are likely to occur at concentrations exceeding 10 mg/m^3 (OSHA Permissible Exposure Limit).

Animal studies suggest that the respiratory tract is susceptible to boron toxicity. Rats exposed to 470 mg/m^3 boron oxide aerosol for 10 weeks developed reddish exudates from their noses, but there were no deaths or signs of lung damage (Wilding et al. 1959). No changes were observed in rats in the 77 mg/m^3 dose group after 24 weeks of exposure, or in dogs exposed to a concentration of 57 mg/m^3 for 23 weeks (Wilding et al. 1959).

Cardiovascular Effects. Animal data are sparse. Rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks showed no histopathological effects in the cardiovascular system (Wilding et al. 1959).

Gastrointestinal Effects. Animal data are sparse. No changes were seen in the gastrointestinal tract of rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

Hematological Effects. Little is known concerning the effects of boron in animals. Rats exposed to aerosols of boron oxide for lo-24 weeks (up to 470 mg/m^3) and dogs for 23 weeks (57 mg/m^3) showed no significant changes in total red and white blood cell count, hemoglobin, hematocrit, and differential count (Wilding et al. 1959).

Musculoskeletal Effects. Animal data are sparse. No histopathological effects of exposure were observed in the femur, rib, and muscle of rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

Renal Effects. Data on the effects of boron in animals are sparse. No renal effects were observed in rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

Dermal/Ocular Effects. Human occupational exposure to a mean concentration of 4.1 mg/m^3 (as boron oxide and boric acid dust) produced eye irritation following chronic exposures in workers employed for an average of 11 years (Garabrant et al. 1984, 1985).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to boron.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to boron. Adverse effects were not found on the brain of rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to boron.

2.2.1.6 Reproductive Effects

Limited data were located regarding reproductive effects in humans after inhalation exposure to boron. One study was reported involving occupational exposure (10 years or greater) to boron aerosols (22-80 mg/m^3) in males engaged in the production of boric acids (Tarasenko et al. 1972). The study group was small, consisting of 28 men. Low sperm counts, reduced sperm motility and elevated fructose content of seminal fluids were observed.

In animals, no effects were found on the ovary or testes of rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

2.2.1.7 Genotoxic Effects

No studies were located regarding the genotoxic effects in humans or animals after inhalation exposure to boron. Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to boron.

2.2.2 Oral Exposure

2.2.2.1 Death

Studies in humans, particularly infants, show that boron (as boric acid) can be lethal following ingestion. Infants who ingested formula accidentally prepared with 2.5% aqueous solution of boric acid died within 3 days after exposure (Wong et al. 1964). It was estimated that the amount of boric acid consumed ranged from 4.51 to 14 g. Although 5 of 11 infants died, the authors provided histopathological data and weights for only 2 infants who had ingested 9.25 g (505 mg boron/kg/day) and 14 g (765 mg boron/kg/day) (Wong et al. 1964). Infants became lethargic and developed vomiting and diarrhea.

Degenerative changes were seen in the liver, kidney, and brain. Acute exposure to dose levels of 895 mg boron/kg as boric acid was not lethal in one adult (Linden et al. 1986).

In animals, boron (as boric acid and borax) is lethal following acute, intermediate, and chronic oral exposures. Estimates of oral LD,, in rats were 898 and 642 mg boron/kg (as boric acid and borax, respectively) (Smyth et al. 1969) and 510 and 550 mg boron/kg as borax and boric acid (Weir and Fisher 1972). No deaths were reported in dogs exposed to 696 mg boron/kg as boric acid and 738 mg boron/kg as borax (Weir and Fisher 1972). In a 14-day repeated-dose feeding study in male mice, doses of 2,251 and 3,671 mg boron/kg/day (as boric acid) were lethal in 20% and 60% of males, respectively (NTP 1987). The mice were lethargic and the spleen, liver, and renal medullae were discolored. Hyperplasia and dysplasia of the forestomach were also observed (NTP 1987).

Survival was also reduced in mice following intermediate-duration exposure. Males (10%) died after exposure to a dose of 288 mg boron/kg/day (as boric acid) in the diet, while 80% of males and 60% of females died at 577 mg boron/kg/day (NTP 1987). Hyperkeratosis and/or acanthosis in the stomach and extramedullary hematopoiesis of the spleen in both sexes were observed at the highest dose tested (577 mg boron/kg/day). There was 100% mortality in rats fed 263 mg boron/kg/day for 90 days (Weir and Fisher 1972). Congestion of liver and kidneys, small gonads, and brain swelling were reported. When male mice consumed 48 and 96 mg boron/kg/day (as boric acid) for 103 weeks, mortality *was* 40% and 56%, respectively, compared to 18% in untreated controls (NTP 1987). No clinical signs were reported; however, boron caused increased incidence of testicular atrophy and interstitial hyperplasia. Mortality in female mice was 30% and 24% (48 and 96 mg boron/kg/day) compared to 34% in the untreated controls (NTP 1987).

The LD_{50} values and the highest NOAEL values in animals and the lowest level at which death was reported in humans and the duration categories are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory effects in animals or cardiovascular or musculoskeletal effects in humans or animals after oral exposure to boron.

Information on respiratory, gastrointestinal, hematological, hepatic, renal, and dermal/ocular effects is discussed below. The highest NOAEL values and all reliable LOAEL values for these systemic effects for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Widespread vascular congestion and hemorrhages in the lungs were reported in one infant who ingested 505 mg boron/kg/day (Wong et al. 1964).

TABLE 2-2. Levels of Significant Exposure to Boron and Compounds - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Human	(F)	3-5 d				505 (increased mortality)	Wong et al. 1964	BA
2	Rat	(F)	1 d				550 (LD50)	Weir and Fisher 1972	BA
3	Rat	(W)	1 d				642 (LD50)	Smyth et al. 1969	BX
4	Rat	(F)	1 d				510 (LD50)	Weir and Fisher 1972	BX
5	Rat	(W)	1 d				898 (LD50)	Smyth et al. 1969	BA
6	Mouse	(F)	14 d				2251 (increased mortality)	NTP 1987	BA
7	Dog	(C)	1 d		738			Weir and Fisher 1972	BX
8	Dog	(C)	1 d		696			Weir and Fisher 1972	BA
Systemic									
9	Human	(F)	3-5 d	Resp			505 (vascular congestion, hemorrhage in infants)	Wong et al. 1964	BA
				Hepatic			505 (parenchymatous degeneration, jaundice, fatty changes, congestion in infants)		
				Renal			765 (parenchymatous degeneration, reduced urine output, protein in urine in infants)		
				Derm/oc		505 (extensive shedding of skin)			

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
10	Human	(F)	3-5 d	Gastro		184 (vomiting, diarrhea in infants)		Wong et al. 1964	BA
				Derm/oc		505 (erythema, desquamation in infants)			
11	Human	(F)	1 d	Gastro		241 (vomiting, diarrhea)		Linden et al. 1986	BA
12	Mouse	(F)	14 d	Gastro		2251 (gastric hyperplasia and dysplasia)		NTP 1987	BA
Neurological									
13	Human	(F)	3-5 d				505 (perivascular hemorrhage, congestion, thrombosis, edema in infants)	Wong et al. 1964	BA
INTERMEDIATE EXPOSURE									
Death									
14	Rat	(F)	90 d				263 (100% mortality)	Weir and Fisher 1972	BX
15	Rat	(F)	90 d				263 (100% mortality)	Weir and Fisher 1972	BA
16	Mouse	(F)	13 wk				144 (increased mortality)	NTP 1987	BA
Systemic									
17	Rat	(F)	90 d	Other	88			Weir and Fisher 1972	BX
18	Rat	(W)	3-14 wk	Hepatic	20.8			Settimi et al. 1982	BX
19	Rat	(W)	70 d	Other		23.7 (decreased body and spleen weights)		Seal and Weeth 1980	BX

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
20	Rat	(F)	90 d	Other		88 (decreased body weight)		Weir and Fisher 1972	BA
21	Dog	(F)	90 d	Other	44			Weir and Fisher 1972	BA
22	Dog	(F)	90 d	Hemato	4.4	44 (decreased packed cell volume and hemoglobin)		Weir and Fisher 1972	BX
Neurological									
23	Rat	(W)	3-14 wk		20.8			Settimi et al. 1982	BX
Developmental									
24	Rat	(F)	20 d			13.6[b] (reduced fetal weight)	28.4 (rib cage defects, increased resorptions)	Heindel et al. 1991	BA
25	Mouse	(F)	17 d		43.4	79 (reduced fetal body weight)	175.3 (skeletal effects, increased resorptions)	Heindel et al. 1991	BA
Reproductive									
26	Rat	(F)	30-60 d		50		100 (testicular atrophy, decreased enzymes)	Lee et al. 1978	BX
27	Rat	(W)	90 d		0.6			Dixon et al. 1976	BX
28	Rat	(F)	90 d			26 (partial testicular atrophy)	88 (complete atrophy of testes)	Weir and Fisher 1972	BA
29	Rat	(F)	60 d		25	50 (reduced testicular enzymes, reduced testicular and epididymal weight)		Dixon et al. 1979	BX

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
30	Rat	(F)	90 d			26 (partial testicular atrophy)	88 (complete atrophy of testes)	Weir and Fisher 1972	BX
31	Rat	(W)	70 d			44.7 (impaired spermatogenesis)		Seal and Weeth 1980	BX
32	Mouse	(F)	13 wk				288 (degeneration or atrophy of seminiferous tubules)	NTP 1987	BA
33	Mouse	(F)	27 wk		26.5	111 (impaired spermatogenesis, degeneration of seminiferous tubules)		NIEHS 1990	BA
34	Dog	(F)	38 wk			29 (testicular atrophy, spermatogenic arrest)		Weir and Fisher 1972	BX
35	Dog	(F)	90 d		4.4	44 (severe testicular atrophy)		Weir and Fisher 1972	BX
36	Dog	(F)	38 wk			29 (testicular atrophy, spermatogenic arrest)		Weir and Fisher 1972	BA
37	Dog	(F)	90 d		4.4	44 (severe testicular atrophy)		Weir and Fisher 1972	BA
CHRONIC EXPOSURE									
Death									
38	Mouse	(F)	103 wk				48 (40% mortality)	NTP 1987	BA
Reproductive									
39	Rat	(F)	2 yr		17.5		58.5 (atrophy of testes, decreased testes weight)	Weir and Fisher 1972	BX

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
40	Rat	(F)	3 gen		17.5		58.5 (atrophy of testes, decreased ovulation)	Weir and Fisher 1972	BA
41	Rat	(F)	3 gen		17.5		58.5 (atrophy of testes, decreased ovulation)	Weir and Fisher 1972	BX
42	Rat	(F)	2 yr		17.5		58.5 (atrophy of seminiferous tubule epithelium, decreased tubule size, decreased testicular weight)	Weir and Fisher 1972	BA
43	Mouse	(F)	103 wk		48		96 (testicular atrophy, interstitial hyperplasia)	NTP 1987	BA
44	Dog	(F)	2 yr		8.75			Weir and Fisher 1972	BX
45	Dog	(F)	2 yr		8.75			Weir and Fisher 1972	BA

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate oral MRL of 0.01 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

BA = boric acid; BX = borax; (C) = capsule; d = day(s); Derm/oc = dermal/ocular; (F) = feed; Gastro = gastrointestinal; gen = generation; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); yr = year(s)

FIGURE 2-2. Levels of Significant Exposure to Boron and Compounds – Oral

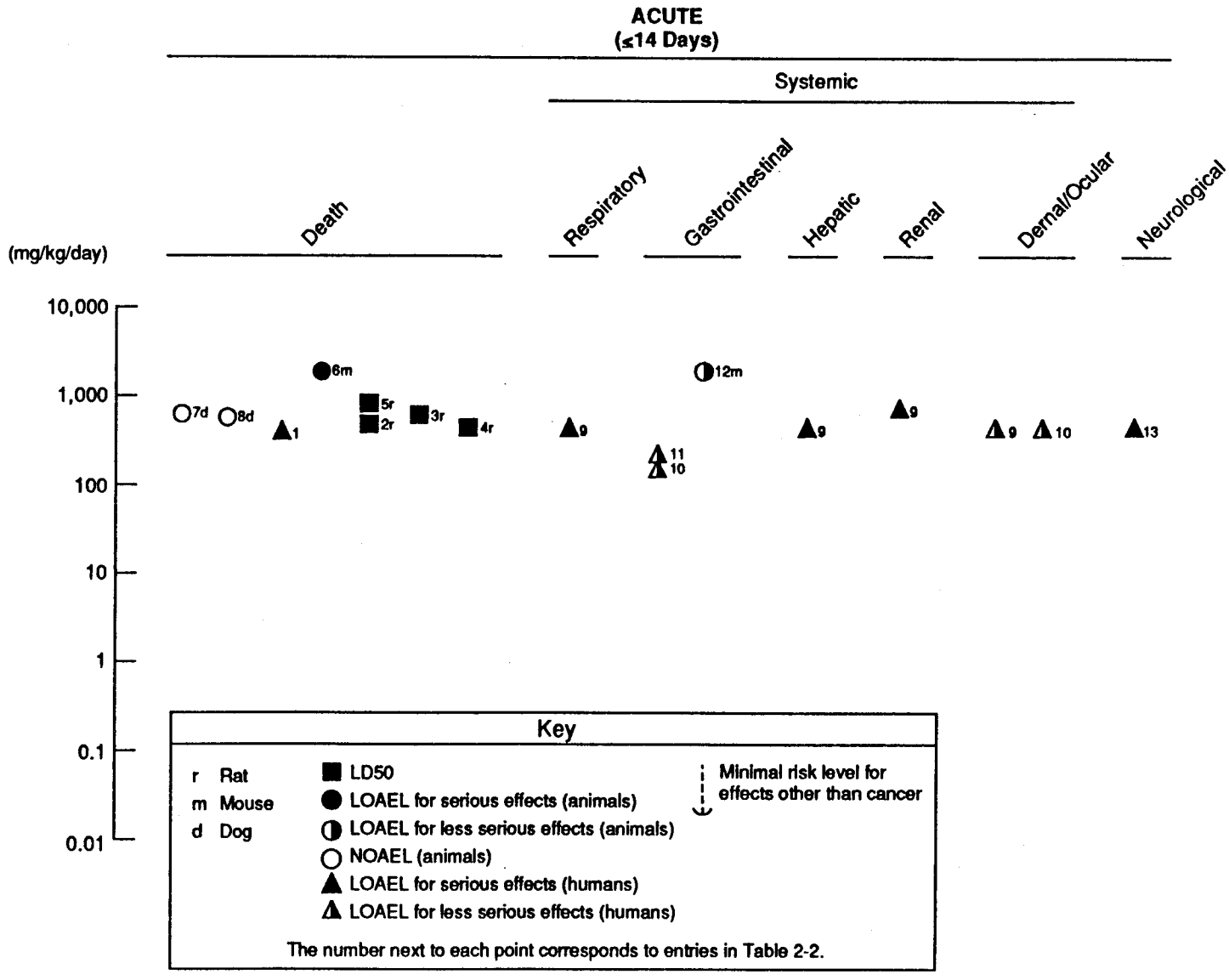


FIGURE 2-2 (Continued)

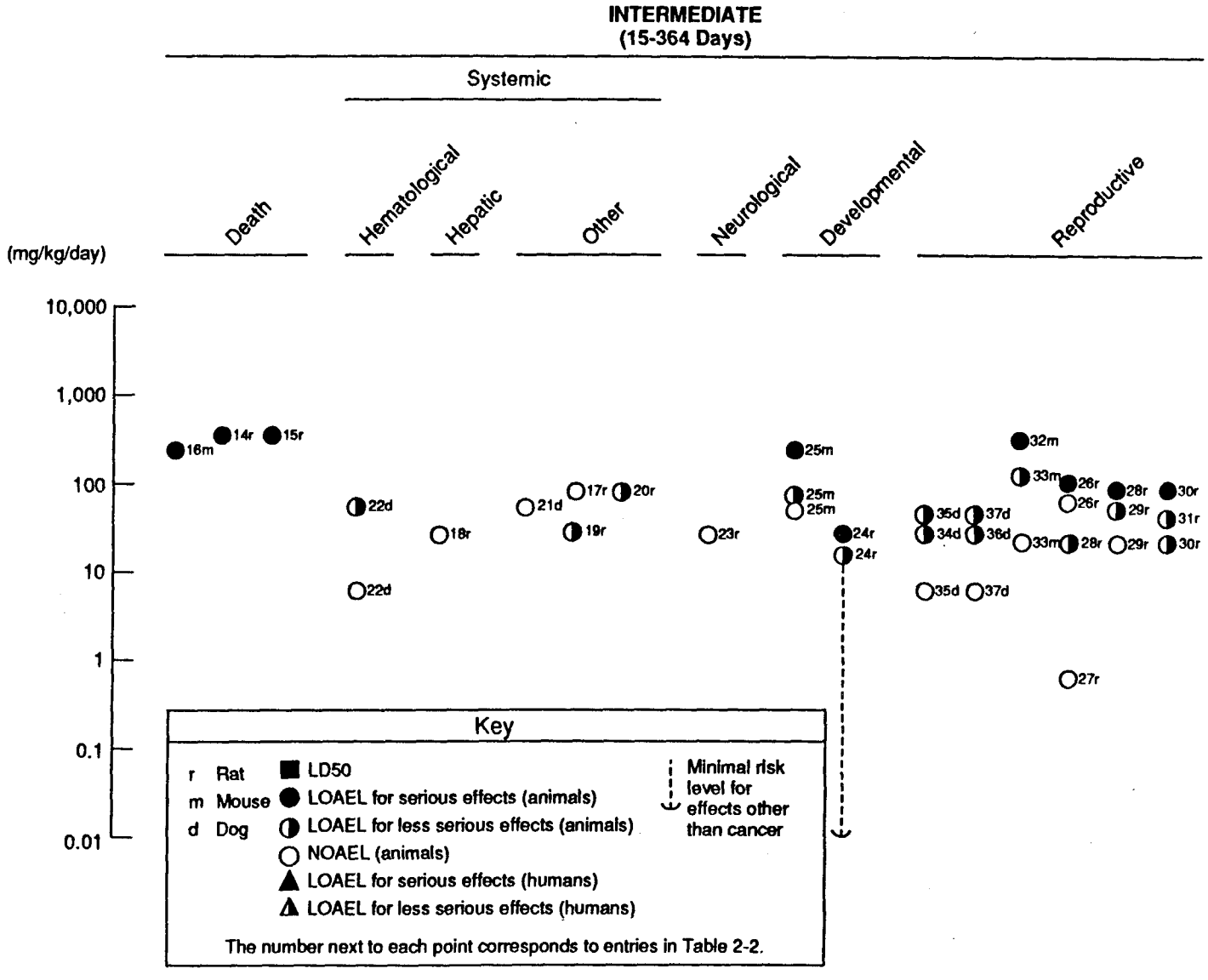
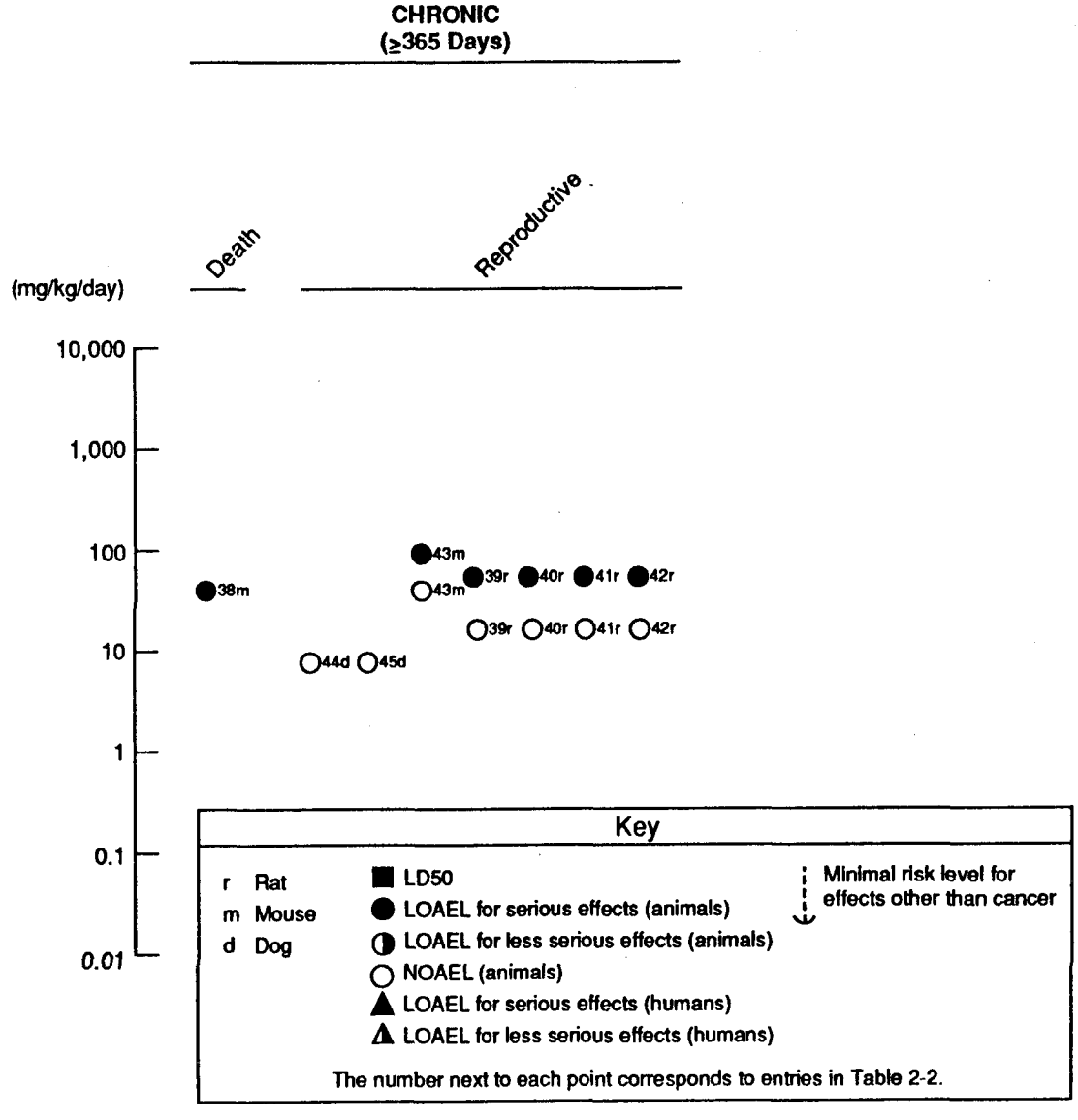


FIGURE 2-2 (Continued)



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Gastrointestinal Effects. Ingestion of boron in humans can cause gastrointestinal effects. Nausea, persistent vomiting, diarrhea, and colicky abdominal pain in infants were associated with acute ingestion of a total of 184 mg boron/kg/day or greater (based on 1.9 kg body weight) as boric acid which was accidently incorporated in infant formula (Wong et al. 1964). Vomiting was the only sign-of boron toxicity in two adult females who had ingested 241 mg boron/kg/day as boric acid in a fungicide and 895 mg boron/kg of a boric acid-containing insecticide in a suicide attempt, The subjects were hospitalized for 24-96 hours and did not develop further symptoms following release (Linden et al. 1986).

Hematological Effects. Two male and three female dogs fed 44 mg boron/kg/day as borax had decreased packed cell volume and hemoglobin values. Erythrocyte count, total and differential leucocyte counts were comparable to control levels (Weir and Fisher 1972).

Hepatic Effects. Case reports in humans suggest that the liver is susceptible to boron toxicity at high dose levels (Wong et al. 1964). Jaundice has been reported, and there were mild alterations at histological examination in infants who ingested 505 or 765 mg boron/kg/day as boric acid (accidentally incorporated in infant formula) for 3-5 days (Wong et al. 1964). In the same incident, congestion and fatty changes were observed, and there was parenchymatous degeneration in newborn infants who ingested 505 or 765 mg boron/kg as boric acid for 3-5 days (Wong et al. 1964).

In rats given approximately 20.8 mg boron/kg/day as borax in drinking water, NADPH-cytochrome C reductase activity and cytochrome b, content decreased in the liver microsomal fraction after 10 and 14 weeks (Settimi et al. 1982). There was also a reduction in the cytochrome P-450 concentration detected at 14 weeks (Settimi et al. 1982).

Renal Effects. Human case reports involving high accidental ingestion levels show that boron can cause injury to the kidney. Degenerative changes in parenchymal cells with oliguria and albuminuria have been demonstrated in two newborn infants after ingestion of 505 and 765 mg boron/kg/day as boric acid in an evaporated milk formula over a period of 3-5 days (Wong et al. 1964).

Dermal/Ocular Effects. Skin effects can occur following ingestion of boron (as boric acid) in humans. Extensive exfoliative dermatitis began in infants as an erythema involving palms, soles, and buttocks. It eventually became generalized with subsequent bulbous formation, massive desquamation, and sloughing (Wong et al. 1964). These changes were associated with ingestion of 505 mg boron/kg/day; however, skin lesions were lacking following ingestion of 765 mg boron/kg/day. Similarly, extensive erythema with desquamation was observed in an adult who ingested boric acid powder (Schillinger et al. 1982). The exact amount ingested was not stated. However, 14 g (equivalent to 22.5 mg boron/kg based on 109 kg body weight) was measured as missing from a container from which the patient admitted consuming half its contents.

In animals, rats fed 88 and 263 mg boron/kg/day as borax or boric acid had inflamed eyes and skin desquamations on the paws and tails (Weir and Fisher 1972).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to boron.

2.2.2.4 Neurological Effects

Case reports in humans have indicated neurological effects after accidental ingestion of high levels of boron (as boric acid). Newborn infants who ingested 4.5-14 g boric acid showed central nervous system involvement manifested by headache, tremors, restlessness, and convulsions followed by weakness and coma (Wong et al. 1964). Histological examination of 2 of 11 infants revealed congestion and edema of brain and meninges with perivascular hemorrhage and intravascular thrombosis at a dose ≥505 mg boron/kg/day (Wong et al. 1964). Seizure disorders have been associated with boron exposures (as borax) in infants who ingested 4-30 g borax for 4-10 weeks (O'Sullivan and Taylor 1983) and 9-125 g borax for 5-12 weeks (Gordon et al. 1973). Estimates of boron consumption could not be determined since the authors did not provide data on kilogram body weights. Blood boron levels in patients who ingested borax ranged from 2.6 to 8.5 μg/mL (O'Sullivan and Taylor 1983). In one infant with a seizure disorder who ingested borax for 3 months, the blood boron level was 1.64 mg/100 mL (Gordon et al. 1973).

In rats, exposure to approximately 20.8 mg boron/kg/day as borax (based on weight of 0.35 kg and average water consumption of 20.7 mL) in drinking water for up to 14 weeks caused increased cerebral succinate dehydrogenase activity after 10 and 14 weeks of exposure (Settimi et al. 1982). Increased RNA concentration and increased acid proteinase activity in brain occurred after 14 weeks (Settimi et al. 1982).

All LOAEL values for neurological effects in humans and animals are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to boron.

In animals, fetotoxicity was observed in rats and mice The average fetal body weight per litter in rats was reduced in pups of dams administered 13.6 mg boron/kg/day or greater (78 mg/kg/day boric acid) on gestation days 0 to 20 (Heindel et al. 1991). Similarly, pups of mice administered 79 mg boron/kg/day (452 mg/kg/day boric acid) showed reduced body weight. Boron was also teratogenic in rats and mice. There was agenesis or shortening of rib XIII and the lateral ventricles of the brain were enlarged in rats at dose

levels of 28.4 mg boron/kg/day (163 mg/kg/day boric acid) or greater (Heindel et al. 1991). Skeletal effects were reported at the highest dose tested (175.3 mg boron/kg/day or 1,003 mg/kg/day boric acid) in mice. No effects were observed in the 43.4 mg boron/kg/day (248 mg/kg/day boric acid) dose group (Heindel et al. 1991). Based on a value of 13.6 mg boron/kg/day, an intermediate oral MRL of 0.01 mg/kg/day was calculated as described in the footnote on Table 2-2.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to boron.

Animal studies demonstrated that boron can cause injury after intermediate and chronic exposure to the gonads in animals, especially the testes. Impaired spermatogenesis has been reported in rats administered 300 mg/boron/L as borax (44.7 mg boron/kg/day) in drinking water for 70 days (Seal and Weeth 1980), but no reproductive effects were evident in rats administered up to 6 mg boron/L of borax (0.6 mg boron/kg/day) in drinking water for 90 days (Dixon et al. 1976). While severe testicular atrophy was seen in dogs fed up to 44 mg boron/kg/day (1,750 ppm boron, as borax or boric acid) for 90 days (Weir and Fisher 1972), partial testicular atrophy in rats occurred at a dose of 26 mg boron/kg/day (525 ppm boron) (Weir and Fisher 1972). Degeneration or atrophy of the seminiferous tubules was demonstrated in mice fed 144 mg boron/kg/day as boric acid (5,000 ppm boric acid) (NTP 1987). In rats fed at least 50 mg boron/kg/day (as borax) up to 60 days, there were reduced testicular weight and germinal aplasia at 60 days (Dixon et al. 1979). In the same study, ≥50 mg boron/kg/day caused reduction in hyaluronidase, sorbitol dehydrogenase, and lactic acid dehydrogenase (isoenzyme-X) at 30 days and testicular and epididymal weights were reduced (Dixon et al. 1979).

In contrast, Lee et al. (1978) did not find significant adverse effects in male rats fed 50 mg boron/kg/day (as borax) for 30 and 60 days. Dogs were fed 29 mg boron/kg/day as borax and boric acid (1,170 ppm), respectively in the diet for 38 weeks (Weir and Fisher 1972). Testicular atrophy and spermatogenic arrest were reported. When dogs were administered 8.8 mg boron/kg/day (350 ppm borax or boric acid) for 2 years, no reproductive effects were observed (Weir and Fisher 1972). Reproductive effects were reported in rats following chronic exposure. In rats fed up to 58.5 mg boron/kg/day (as borax or boric acid) for several generations, there was a lack of viable sperm in atrophied testes and ovulation decreased in females (Weir and Fisher 1972). There were testicular atrophy and interstitial hyperplasia in mice that consumed lethal doses (48 and 96 mg boron/kg/day) over a period of 103 weeks. However, the authors did not specify cause of death (NTP 1987). In a 2-generation reproduction mouse study using continuous breeding protocol, there was degeneration of the seminiferous tubules and spermatogenesis was impaired at dose levels of 111 mg boron/kg/day (636 mg/kg/day boric acid) or greater. No effects were observed in the 27 mg boron/kg/day (152 mg/kg/day boric acid) dose group (NIEHS 1990).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in animals and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans and animals after oral exposure to boron. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to boron.

In a life-time bioassay in which male and female $B6C3F_1$ mice consumed 48 mg boron/kg/day or 96 mg boron/kg/day as boric acid in the diet, there was no evidence of carcinogenicity (NTP 1987).

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to boron.

2.2.3.2 Systemic Effects

No studies were located regarding hematological and dermal/ocular effects in humans and respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to boron.

All reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3.

Hematological Effects. Data are sparse in animals. It was reported in Draize and Kelley (1959) that the application of 25-200 mg/kg/day boric acid in aqueous solution did not produce hematological changes when rubbed onto intact skin during a 90-day rabbit study. No quantitative data were provided; therefore, these results could not be evaluated.

Dermal/Ocular Effects. Animal studies show that boron oxide dust can affect the eye and skin. Instillation of boron oxide dust (50 mg) into the eyes of four rabbits produced conjunctivitis (Wilding et al. 1959). Application of 1 g boron oxide dust to a 25 cm^2 area of the skin of four rabbits produced erythema that lasted for 2-3 days (Wilding et al. 1959).

TABLE 2-3. Levels of Significant Exposure to Boron and Compounds - Dermal

Species	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
ACUTE EXPOSURE							
Systemic							
Rabbit	1 d	Derm/oc		13 (conjunctivitis)		Wilding et al. 1959	BO
		Derm/oc		1[a] (erythema)			

[a]Original unit provided by author was 1 g/cm^2.

BO = boron oxide; d = day; Derm/oc = dermal/ocular; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

2. HEALTH EFFECTS

No studies were located regarding the following health effects in humans or animals after dermal exposure to boron:

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer effects in humans or animals after dermal exposure to boron.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No quantitative studies were located regarding absorption in humans or animals after inhalation exposure to boron. Reports of upper respiratory tract symptoms following exposure to boron oxide and boric acid dusts suggest boron can deposit in the upper airway (Garabrant et al. 1984, 1985).

2.3.1.2 Oral Exposure

No quantitative studies were located regarding absorption in humans or animals after oral exposure to boron and compounds. Gastrointestinal absorption was indicated in humans as evident by the urinary recovery of 93.9% of the ingested dose of boric acid when urine samples were calculated over a 96 hour period (Jansen et al. 1984a). Neurological, kidney, and liver damage following ingestion further suggest that boron can be absorbed (Wong et al. 1964).

2.3.1.3 Dermal Exposure

No quantitative studies were located regarding boron absorption in humans or animals after dermal exposure. Urinary excretion studies in humans (Section 2.3.4.3) suggest there is very little absorption of boron through intact skin. Excretion studies (Section 2.3.4.3) in rabbits suggest that boron is readily absorbed following contact with damaged skin (Draize and Kelley 1959).

2.3.2 Distribution

No quantitative studies were located regarding distribution in humans or animals after exposure to boron and compounds by the following routes:

2.3.2.1 Inhalation Exposure
2.3.2.2 Oral Exposure
2.3.2.3 Dermal Exposure

2.3.3 Metabolism

No studies were located regarding metabolism in humans or animals after exposure to boron or boron compounds by the following routes:

2.3.3.1 Inhalation Exposure
2.3.3.2 Oral Exposure
2.3.3.3 Dermal Exposure

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans after inhalation exposure to boron. In rats that inhaled average concentrations of 77 mg/m^3 boron oxide aerosols over a 22 week period, an average of 11.90 mg boron/kg/day was detected in the urine compared to 0.24 mg/kg/day in untreated control groups (Wilding et al. 1959).

2.3.4.2 Oral Exposure

Over 93% of the administered dose was excreted in the urine of six male human volunteers 96 hours after administration of a single oral dose of 1.9 mg boron/kg (as boric acid) (Jansen et al. 1984a). An analysis of nine cases involving boric acid poisoning revealed a mean half-life of 13.4 hours (4-27.8). There was no correlation between half-life and calculated serum boric acid level at t, ($r=0.08$, $p=0.84$) (Litovitz et al. 1988). Boric acid was detected in urine of patients 23 days after a single ingestion (Wang et al. 1964).

In rabbits, 50%-66% of the administered dose was recovered in urine after ingestion of 17.1-119.9 mg boron/kg/day as boric acid (Draize and Kelley 1959).

2.3.4.3 Dermal Exposure

Limited data in humans suggest that very little absorption of boron occurs through intact skin. There was no increase in the urinary excretion of boron in one human subject following the application of 15 g boric acid (37.5 mg boron/kg bw) on the forearm for 4 hours (Draize and Kelley 1959).

Animal studies support human findings. Draize and Kelley (1959) applied 200 mg/kg as boric acid to intact, abraded or burnt, and partially denuded skin of rabbits. Net urinary excretion of boric acid per 24 hours during 4 consecutive days of compound treatment was 1.4, 7.6 and 21.4 mg/kg, respectively (0.25, 1.3, and 3.7 mg boron/kg, respectively).

2.3.4.4. Other Exposure

In eight adult volunteers administered a single dose of boric acid (562-611 mg) by intravenous infusion, 98.7% of the administered dose was recovered in urine 120 hours after injection (Jansen et al. 1984b). Renal blood clearance averaged 39.1 mL/min per 1.73 m^2 surface area in eight adult human subjects administered intravenous injections of 35 mg boron/kg (as sodium pentaborate). Urine boron concentrations on the day of administration averaged 1.19 mg/mL (Farr and Konikowski 1963).

2.4 RELEVANCE TO PUBLIC HEALTH

Estimates of levels of exposure to boron posing minimal risk to humans (MRLs) have been made. These are discussed in Section 2.2 and were based on data believed to be reliable for the most sensitive noncancer effect for each route and exposure duration. No data were located on effects of acuteduration inhalation exposure in humans or animals nor on intermediate-duration inhalation exposure to boron in humans. Available information on intermediate-duration inhalation exposure in animals and chronic-duration inhalation exposure in humans do not reliably identify the most sensitive target organ, No data on effects of acute-duration oral exposure to boron in humans or animals nor on intermediate exposure in humans were located. In animals, prenatal exposure of mice (79 mg boron/kg/day as boric acid) and rats (13.6 mg boron/kg/day as boric acid) during gestation days 0-17 and 0-20 caused developmental effects consisting of reduced fetal body weight or minor skeletal changes and possibly delay in maturation (Heindel et al. 1991). There was degeneration of the seminiferous tubules and impaired spermatogenesis in mice exposed to dose levels of 111 mg boron/kg/day as boric acid for 2 generations (NIEHS 1990). In other studies involving intermediate duration exposure, gonadal damage, primarily in the testes, was evident at dose levels from 26 to 288 mg/kg/day (NTP, 1987; Weir and Fisher 1972), but not at dose levels of 0.6 and 25 mg/kg/day (Dixon et al. 1976, 1979). Exposure of dogs to boron (as boric acid or borax) in the diet for 38 weeks caused testicular atrophy and spermatogenic arrest at dose levels of 29 mg boron/kg/day (Weir and Fisher 1972). Based on a LOAEL value of 13.6 mg boron/kg/day for developmental toxicity, an intermediate oral MRL of 0.01 mg boron/kg/day was derived using an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability). However, testicular effects were reversible within 25 days after compound treatment ceased. No effects were observed in rats fed diets containing doses up to 8.75 mg boron/kg/day) for 2 years (Weir and Fisher 1972). Because developmental toxicity occurred at dose levels less than those for reproductive toxicity, the intermediate MRL based on developmental toxicity'should be protective against reproductive toxicity following chronic

exposure. No data were located on effects of chronic-duration oral exposure in humans. A chronic MRL was not derived. Acute-duration, intermediateduration, and chronic-duration dermal MRLs were not derived for boron due to the lack of an appropriate methodology for the development of dermal MRLs.

No studies have been found regarding immunological effects of boron and compounds in humans or animals.

Death. Human studies have shown that boron can be lethal following short-term exposure. The minimal lethal dose of ingested boron (as boric acid) was reported to be 2-3 g in infants, 5-6 g in children and 15-20 g in adults (Locatelli et al. 1987; Wong et al. 1964). No data were found on the potential for boron to cause death in humans after intermediate and chronic inhalation and oral exposures. Liver, kidney, brain damage, and skin lesions have been found in lethal cases following ingestion of boron, but death has been attributable to respiratory failure. In other studies, chronic dermal exposure to boron in neonates was fatal (Litovitz et al. 1988). There appears to be a differential susceptibility with regard to death in adults. It has been postulated that increased competence of the adult kidney accounts for adult tolerance to boron. Based on these findings, lethality may be an area of concern following neonate exposure to boron.

Animal studies support human findings. Boron was lethal after ingestion for acute, intermediate, and chronic duration exposures (NTP 1987; Smyth et al. 1969; Weir and Fisher 1972).

Systemic Effects

Respiratory Effects. Symptoms of acute irritation of the upper airway were observed at borax and boric acid levels of 4 mg/m^3 or greater (Garabrant et al. 1984, 1985). No adverse respiratory effects were observed in humans following intermediate inhalation exposures. Chronic inhalation exposure caused irritation of the upper respiratory tract (Garabrant et al. 1984, 1985). There were no changes in the FEV_1 and FVC in borax workers (Wegman et al. 1991). Intermediate inhalation exposure in animals caused irritation of the nose (Wilding et al. 1959).

Gastrointestinal Effects. Boron or boron compounds can result in gastrointestinal disorders in humans following acute and intermediate oral exposures. Most of the studies focused on clinical symptoms including vomiting and diarrhea. No data were found on biochemical changes and limited data were provided on histopathological effects. Infants appear to be particularly susceptible to boron toxicity, possibly due to the fact that their detoxifying enzyme systems are immature and there is greater gastrointestinal absorption.

No studies were located in animals regarding gastrointestinal effects following boron exposure.

2. HEALTH EFFECTS

Hepatic Effects. No adverse hepatic effects have been reported in humans or animals following inhalation or dermal exposure to boron or boron compounds. Acute oral exposure in humans caused congestion, fatty changes, and parenchymatous degeneration (Wong et al. 1964). No data were available on biochemical changes. It is not clear how boron affects the liver; however, limited animal data suggest impaired electron transfer and macrometabolism. In studies with rats, boron interfered with flavin metabolism in flavoprotein dependent pathways (Settimi et al. 1982). It is not clear if similar effects will occur in humans.

Renal Effects. No adverse renal effects have been reported in humans or animals following inhalation of boron oxide, boric acid dust, or boron oxide aerosol. Similarly, dermal exposure to boric acid in humans or animals did not adversely affect the kidneys. Renal tubular damage has been observed, and there.was reduced urine output in infants who consumed 505 mg boron/kg in infant formula for 3-5 days (Wong et al. 1964). Since renal effects occurred in only a few cases and there is no confirming evidence in animals, the potential for boron to cause renal effects cannot be conclusively established.

Dermal/Ocular Effects. Human occupational exposure to boron oxide and boric acid dusts in workplace air irritated the eyes (Garabrant et al. 1984). Ingestion of large amounts of boron (505 mg boron/kg as boric acid) caused extensive exfoliative dermatitis in humans (Wong et al. 1964). The application of boric acid on the forearm of human subjects did not affect the skin (Draize and Kelley 1959). Rabbits developed erythema when boron oxide dust was applied to the skin and conjunctivitis was observed following contact with boron oxide dust (Wilding et al. 1959).

Immunological Effects. No studies were located regarding the effects of boron on the immune system in humans or animals after inhalation, oral, or dermal exposure. In the absence of effects on target organs and direct tests on immune function, the potential for boron to cause immunological effects in humans cannot be conclusively evaluated.

Neurological Effects. No adverse neurological effects have been observed in humans or animals following inhalation or dermal exposure. Acute and intermediate oral exposures to boron and boron compounds caused various neurological responses in humans. Degenerative changes in brain neurons which may have been an agonal effect were reported in one infant who consumed 505 mg boron/kg as boric acid for 3 days (Wong et al. 1964). At a higher dose (765 mg boron/kg), there was extensive vascular congestion, widespread perivascular hemorrhage, and intravascular thrombosis in another infant who ingested infant formula containing boric acid for 5 days (Wong et al. 1964). Biochemical changes have also been found. Cerebral succinate dehydrogenase activity was increased in rats that ingested borate in drinking water for lo-14 weeks, suggesting alteration in electron-transfer in the mitochondrial respiratory chain (Settimi et al. 1982). Increased RNA concentration and increased acid proteinase activity in the brain also occurred (Settimi et al. 1982). Altered metabolism and brain tissue redox state suggest changes in protein metabolism.

Based on these considerations, neurological damage is an area of concern following exposure to boron at toxic levels.

Developmental Effects. Developmental changes in rats and mice have been observed in offspring of dams exposed to 28.4 mg boron/kg/day and 175.3 mg boron/kg/day, respectively (Heindel et al. 1991). These effects have been observed at dose levels in the same range as those producing changes in spermatogenesis. No epidemiological studies were located regarding the effects of boron on the developing fetus. Although human data are lacking and there are no direct quantitative studies regarding placental transfer of boron, positive responses in two animal species suggest that developmental toxicity may be an area of concern in humans following exposure to boron. The LOAEL value of 13.6 mg boron/kg/day (Heindel et al. 1991) was used to calculate an intermediate oral MRL of 0.01 mg/kg/day as described in the footnote in Table 2-2.

Reproductive Effects. A study of 28 male workers exposed to borate aerosols during the production of boric acid revealed low sperm counts in six of these workers (Tarasenko et al. 1972). The authors reported exposure concentrations ranging from 22 to 80 mg/m^3. The overall reliability of these data is reduced due to the small study group, It should also be noted that low sperm count is a naturally occurring phenomenon. No studies were located regarding reproductive effects in humans after oral or dermal exposure.

In animals, boron affects gonads in dogs, rats, and mice. The testes are particularly susceptible after intermediate ingestion (44 and 29 mg boron/kg/day, respectively) (Seal and Weeth 1980; Weir and Fisher 1972). Following chronic oral exposure, no effects were observed at a dose of 8.75 mg boron/kg/day (Weir and Fisher 1972). In spite of the absence of reliable human data, limited evidence of reproductive effects in animals suggest that reproductive toxicity may be an area of concern following boron exposure in humans.

Genotoxic Effects. No studies were located regarding genotoxic effects of boron by inhalation, oral, or dermal exposure in humans and animals. Results were negative in bacterial assays and in the in vitro (Table 2-4) mammalian assays, including tests for chromosomal aberrations and gene mutation. Existing data suggest that genotoxicity is not an area of concern following exposure to boron in humans.

Cancer. No epidemiological studies were located associating cancer and boron exposure. In mice fed boron (as boric acid) for 103 weeks, the number of tumors observed did not differ significantly from untreated control levels (NTP 1987). In the absence of human data and studies from other animal species, and the lack of evidence of mutagenic activity, the carcinogenic potential of boron in humans cannot be determined conclusively.

TABLE 2-4. Genotoxicity of Boron *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	-	-	Haworth et al. 1983
S. typhimurium	Gene mutation	-	-	Benson et al. 1984
Escherichia coli	Gene mutation	-	-	Demerec et al. 1951
S. typhimurium	Gene mutation	-	-	NTP 1987
Mammalian cells:				
Mouse lymphoma	Gene mutation	-	-	NTP 1987
Chinese hamster ovary	Chromosomal aberration	-	-	NTP 1987

- = negative result

2. HEALTH EFFECTS

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989). A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to boron and compounds are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by boron and compounds are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Boron

Boron in blood and urine can be used as an indicator of exposure to boron. Normal dietary concentrations of boron in the blood of humans range from 0 to 1.25 pg/mL in children and infants (Fisher and Freimuth 1958; O'Sullivan and Taylor 1983). Boron blood levels (reported as borate) of

20-150 μg/mL have been associated with adverse systemic effects in infants who ingested boric acid in infant formula (Wong et al. 1964). Boron concentrations, expressed as borate, reported in fatal cases vary from 200 to 1,600 μg/mL in infants (Wong et al. 1964). In adults, a serum boron level (as boric acid) of 2,320 μg/mL was not associated with significant toxicity (Linden et al. 1986).

Urinary excretion levels can also be useful indicators of elevated total body burden of boron. Concentrations of boron in the normal population range from 0.07 to 0.15 mg/100 mL (Vignec and Ellis 1954) and 0.004 to 0.66 mg/100 mL (Imbus et al, 1963). In one infant, the urine contained 13.9 mg boron/L as borax or 1.38 mg boron/ml of boric acid following ingestion of a borax and honey mixture over a period of 12 weeks (Gordon et al. 1973). Virtually complete urinary excretion was indicated by the recovery of 93.9% (over a 96-hour collection period) of a boric acid solution ingested by three human volunteers (Jansen et al. 1984a).

Neurological, dermal, gastrointestinal, liver, and kidney effects in humans have been associated with exposure to boron. Studies in animals have demonstrated gonadal injury. Various clinical and biochemical tests exist that may provide useful information on exposure. However, similar effects are caused by a variety of other substances and are, therefore, not specific for boron exposure.

2.5.2 Biomarkers Used to Characterize Effects Caused by Boron

Central nervous system injury, gastrointestinal effects, and skin damage are characteristic manifestations of boron toxicity in humans. Liver and kidneys in humans and testes in animals can also be affected. Various clinical and biochemical changes associated with these effects may be measured to detect the extent of exposure to boron. There is no single biological indicator of boron exposure; consequently, several parameters must be measured including boron levels in urine and blood and biochemical changes for systemic and neurological effects.

Neurological damage has been reported in humans. Neurological effects reported in humans have focused primarily on histopathological alterations. No data were provided on biochemical changes. In animals, testicular atrophy and reduced sperm production have been demonstrated following chronic boron exposure. There are clinical and biochemical tests to detect neurological and gonadal injury, but these are not specific for boron exposure. Sparse data in animals suggest some biochemical changes; for instance, cerebral succinate dehydrogenase was increased in rats after boron exposure. Animal data further demonstrate biochemical alterations following gonadal injury. Dose-dependent reduction in hyaluronidase, sorbitol dehydrogenase, and lactic acid dehydrogenase (isoenzyme-X) were observed in rats following boron exposure.

2.6 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding the influence of other chemicals on the toxicity of boron.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Neonatal children are unusually susceptible to boron exposure.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to boron. This section is intended to inform the public of existing clinical practice and the status of research concerning such methods. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to boron. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Human exposure to boron may occur by inhalation, ingestion, or dermal contact (see Chapter 5). Boron in the form of boric acid or borate dust is an upper respiratory tract irritant following inhalation and may also irritate the eyes and skin. Ingestion of boron may cause gastrointestinal, neurological, hepatic, renal, and dermal effects (see Section 2.2). General recommendations for reducing absorption of boron following exposure have included removing the exposed individual from the contaminated area and removing the contaminated clothing. If the eyes and skin were exposed, they are flushed with water.

Nausea, vomiting, and diarrhea have been induced by ingestion of boron in humans. Some authors recommend reducing absorption of boron from the gastrointestinal tract by administration of emetics (e.g. syrup of ipecac) and cathartics (e.g. magnesium sulfate) (Stewart and McHugh 1990). Caution should be, however, taken not to induce further damage to the esophageal mucosa or to cause aspiration of the vomit into the lungs during emesis. There is disagreement regarding the efficiency of activated charcoal in preventing absorption of boron from the gastrointestinal tract following oral exposure (Ellenhorn and Barceloux 1988; Stewart and McHugh 1990). It has been suggested that activated charcoal be administered following gastric evacuation, but its effectiveness has not been established (Ellenhorn and Barceloux 1988). Administration of intravenous fluids may be required if severe dehydration or shock develop and local skin care may be necessary if skin desquamation occurs (Stewart and McHugh 1990). In addition, the treatment of boron poisoning may request a control for convulsions.

Elemental boron is not metabolized (see Section 2.3). Studies in human volunteers indicated that most of the administered dose is excreted in the urine within few days (Jansen et al. 1984a).

Saline diuresis has been suggested to further enhance urinary excretion of boron (Goldfrank et al. 1990). Exchange transfusions, peritoneal dialysis, or hemodialysis may be employed to lower plasma boron levels following either acute or chronic intoxication. There are indications that hemodialysis is the most effective of these procedures (Goldfrank et al. 1990; Stewart and McHugh 1990). Additional details regarding treatment of boron intoxication may be found in the cited references.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in,consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of boron is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of boron.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

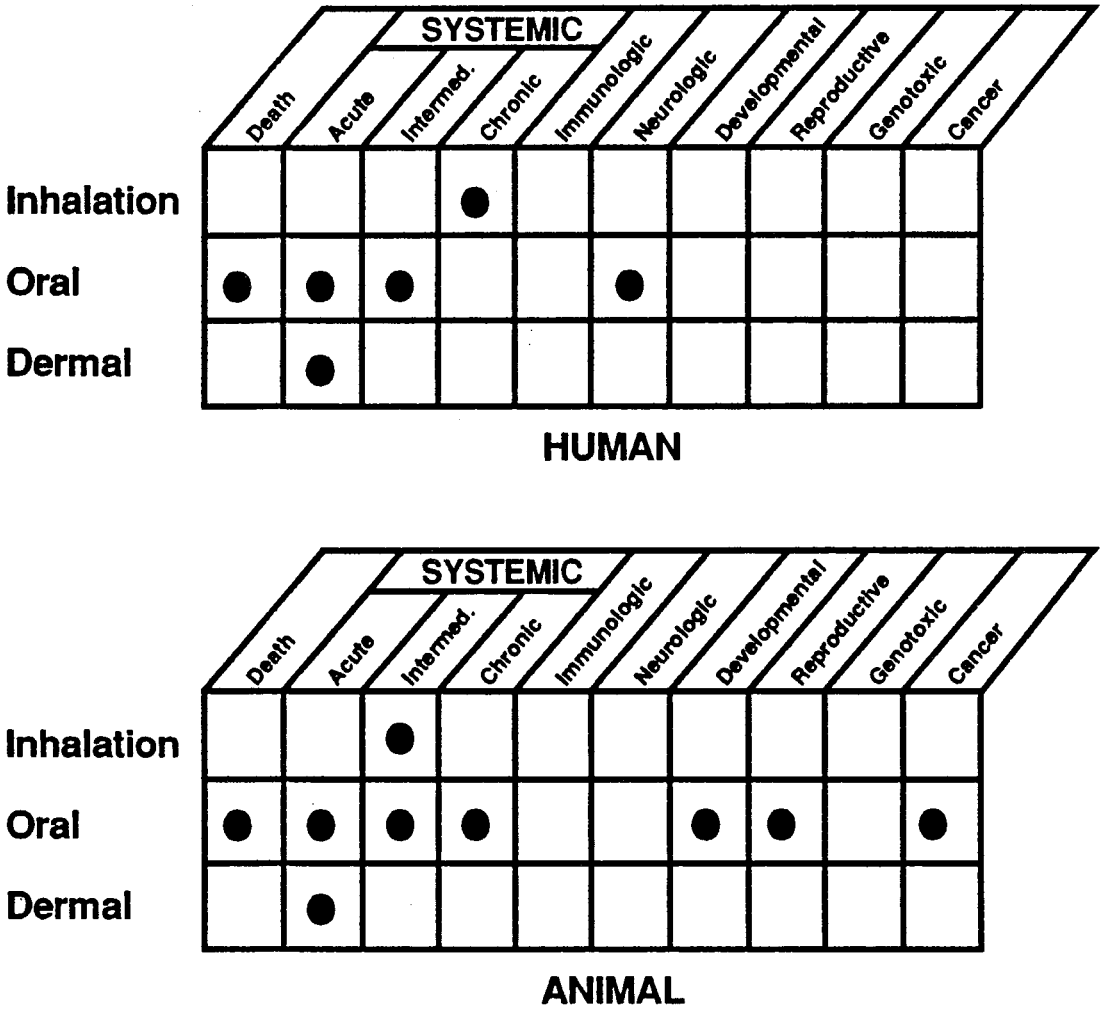
2.9.1 Existing Information on Health Effects of Boron

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to boron are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of boron. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

Most of the information concerning health effects of boron in humans is found in case reports of accidental acute and intermediate ingestion of boron No information was found on effects after chronic ingestion. Those effects associated with inhalation occurred following chronic exposure in the workplace. No information was found on effects of boron after acute and intermediate inhalation exposures. Information on acute dermal exposure exist, but none was found on effects after intermediate and chronic exposures.

In animals, information exists on the acute, intermediate, and chronic ingestion of boron. Those effects associated with inhalation of boron occurred following intermediate exposures. No information was found on health effects of boron after acute and chronic inhalation exposures. Boron does cause health effects following acute dermal exposure. No information was found on health effects after intermediate and chronic dermal exposures.

FIGURE 2-3. Existing Information on Health Effects of Boron



● Existing Studies

2.9.2 Data Needs

Acute-Duration Exposure. There are data indicating mild upper respiratory irritation in humans from acute inhalation of borate dusts (Wegman et al. 1991). Information on the effects of a single oral exposure to boron compounds in humans and animals have provided data on lethal effects, while injury to the lungs, brain, kidneys, and liver have been reported in infants (NTP 1987; Smyth et al. 1969; Weir and Fisher 1972; Wong et al. 1964). Many of the human data are derived from case reports involving toxic effects in infants. No adverse health effects have been demonstrated in humans after dermal exposure. However, dermal/ocular effects have been associated with dermal exposure in animals (Wilding et al. 1959). The irritation effects observed were probably due to the exothermic rehydration reaction of the anhydride boron oxide. While existing data are sufficient to identify target organs, additional oral and dermal studies may clarify dose-response relationships in target tissues and identify a threshold for systemic effects due to a single-dose exposure. Human and animal data were not sufficient to derive acute oral and inhalation MRLs. Existing data provide qualitative evidence of toxic effects; however, data gaps exist relative to concentration and effects in the target tissues.

Intermediate-Duration Exposure. No studies were located in humans after intermediate exposure to boron compounds by any route of exposure. Borates are not absorbed through intact skin (Draize and Kelley 1959). No studies were available on dermal or inhalation exposure in animals; however, lethal effects and injury to the gonads, particularly the testes, have been demonstrated after oral exposure (Dixon et al. 1979; Lee et al. 1978; NIEHS 1990b; NTP 1987; Seal and Weeth 1980; Weir and Fisher 1972). Data suggest differences in sensitivity to boron compounds among animal species, with dogs more sensitive than rats or mice (Weir and Fisher 1972). Developmental effects were reported in mice and rats after oral exposure (Heindel et al. 1991). Data are sufficient to develop an intermediate oral MKL. The MRL was based on developmental toxicity in rats (Heindel et al. 1991). Although the MEL value is lower than the average daily intake of boron, it should be noted that recommended daily allowance levels have not been established for boron. Further studies by other routes of exposure would be useful in confirming target tissues (e.g., testes) and effects on the fetus identified by the primary exposure route. Also, these data may be used to further assess the level of confidence in current NOAEL and LOAEL values. Additional data may also provide some insight into the basis for differential susceptibility among species which may be useful in assessing potential human risk.

Chronic-Duration Exposure and Cancer. Limited epidemiologic studies conducted in humans demonstrated that borate dust can affect the upper respiratory tract and cause eye irritation following inhalation (Gabarant et al. 1984, 1985). Data were not sufficient to derive a chronic-duration MEL. No studies were found on oral and dermal exposures in humans. Oral studies in animals demonstrated injury to the gonads and to the developing fetus (NIEHS 1990a; NTP 1987; Weir and Fisher 1972). Existing oral studies are sufficient to rule out effects on other organ systems or tissues (NTP

1987; Weir and Fisher 1972). No studies were found on chronic dermal and inhalation data in animals. Additional studies are needed to identify critical effect levels. Although data are sufficient to develop a chronic oral MRL, a value was not derived. Because developmental toxicity occurred at dose levels less than those for reproductive effects, the intermediate MRL, which is based on developmental toxicity, should be protective against reproductive toxicity following chronic exposure. Additional studies would be useful in assessing the level of confidence in existing NOAEL and LOAEL values.

No epidemiologic studies have been conducted in humans regarding boron exposure and cancer. Well-designed and well-conducted case control or cohort studies would be useful in assessing risk to exposed humans. A long-term oral bioassay in mice was negative. No studies on chronic dermal or inhalation exposure evaluating carcinogenic potential in animals are available. The absence of effects in one species is not sufficient to rule out the potential to cause cancer. Additional chronic studies of other species and various doses would increase the level of confidence in results reported in existing studies.

Genotoxicity. No in vivo human data were located. Bacterial and limited mammalian assays were negative (Benson et al. 1984; Demerec et al. 1951; Haworth et al. 1983; NTP 1987). Considering the absence of mutagenic effects in bacterial and mammalian tests evaluating gene mutation and chromosomal aberrations, genotoxicity may not be an area of concern in humans. Based on existing data, additional studies are not needed at this time.

Reproductive Toxicity. No studies were found on the effects of boron compounds on the reproductive system in humans by any route of exposure. Oral studies in animals demonstrated injury to gonads, particularly the testes (Dixon et al. 1979; Lee et al. 1978; NIEHS 1990; Seal and Weeth 1980; Weir and Fisher 1972). No studies were found on chronic dermal and inhalation studies in animals. Sufficient data exist on the potential for boron compounds to affect male reproductive organs in animals (NIEHS 1990; NTP 1987; Weir and Fisher 1972). Data suggest that the severity of effects are species specific (Weir and Fisher 1972). Additional studies would be useful to clarify dose response relationships. Data suggest the female reproductive system is less susceptible and is affected only at very high dose levels (NIEHS 1990; NTP 1987; Weir and Fisher 1972). Additional studies evaluating reproductive effects in females may not be needed at this time.

Developmental Toxicity. No studies were found on the developmental effects of boron and compounds in humans following inhalation, oral, or dermal exposure. No data are available on the ability of boron to cross the placenta or accumulate in fetal tissue. Studies in rats and mice indicate delayed development and structural defects, primarily in the rib cage, following continuous oral exposure in the diet during pregnancy (Heindel et al. 1991). Existing animal data suggest additional testing would be useful in assessing potential risk to humans.

Immunotoxicity. No studies were found in humans or animals on the effects of boron on the immune system by any route of exposure. Results of chronic studies do not suggest that the immune system is a potential target for boron toxicity. Additional studies are not needed at this time.

Neurotoxicity. Case reports in humans, primarily infants, indicate that neurological effects occur after ingestion of boron at high dose levels (Wong et al. 1964). Degenerative changes in brain cells, perivascular hemorrhage, and intravascular thrombosis have been reported in fatal case reports in infants, but neurochemical or neurophysiological changes have not been reported (Settimi et al. 1982; Wong et al. 1964). No studies are available on neurotoxic effects of boron following inhalation or dermal exposure in humans. Animal data are limited to increased brain enzyme activity (Settimi et al. 1982), but no histopathological data are available. Since data on effects are limited primarily to acute oral exposures at high dose levels, additional studies in animals evaluating other dose levels and exposure durations would be useful in evaluating potential risk to humans who may be exposed to low levels of boron compounds near hazardous waste sites.

Epidemiological and Human Dosimetry Studies. Information exists on the adverse health effects of boron compounds in humans. Studies of workers exposed to boron compounds demonstrated that boron can cause mild irritation of the eyes and respiratory tract (Garabrant et al. 1984, 1985). Other human studies involve case reports of accidental or intentional ingestion of large quantities of boron compounds (Litovitz et al. 1988; Locatelli et al. 1987). The studies identified key health effects (lung, kidney, brain, and liver) associated with boron exposure (Wong et al. 1984). Animal studies indicated the testes as a target tissue, Epidemiological studies of the birth rate of occupationally-exposed workers is currently underway at a major U.S. borate production facility (U.S. Borax and Chemical Corporation 1991).

Biomarkers of Exposure and Effect. Blood and urine borate concentrations are useful biomarkers of exposure (Jansen et al. 1984a; Litovitz et al. 1988). The gastrointestinal tract, skin, and brain are principal target organs following boron exposure in humans. Studies in animals demonstrate that boron compounds can also cause gonadal injury, particularly to the testes (Weir and Fisher 1972). Existing animal studies have established this effect as the most sensitive endpoint following oral exposure. Studies to determine other biomarkers would be useful in assessing the potential human health risk.

Absorption, Distribution, Metabolism, and Excretion. No quantitative information is available on the absorption, distribution, and metabolism of boron compounds; however, there are studies on the excretion of boron following oral (Jansen et al. 1984a; Litovitz et al. 1988) and inhalation (Wilding et al. 1959) exposures and after dermal exposure (Draize and Kelley 1959). Since data on toxicokinetics of boron are limited, additional studies are needed by all routes of exposure that will provide data on absorption rates, extent of conversion in the body and amount and rate of accumulation in various tissues. Limited data from oral and dermal studies suggest that boron

is primarily excreted in urine. Since boron can deposit in the upper respiratory tract, additional excretion studies by this route would be useful in determining if excretion patterns are similar across all routes of exposure.

Comparative Toxicokinetics. Existing evidence from human and animal studies do not indicate whether or not boron compounds affect the same target tissues. Animal studies indicate the testes as a target tissue (Dixon et al. 1979; Lee et al. 1978; NIEHS 1990; Seal and Weeth 1980; Weir and Fisher 1972). Data suggest differences in species sensitivity, with dogs more sensitive than rats and mice (Weir and Fisher 1972). No data have been found on potential reproductive effects of boron and compounds in humans. Data exist on excretion of boron compounds. Based on excretion studies, boron compounds are absorbed by the gastrointestinal tract. There are no available quantitative toxicokinetics data on absorption, distribution, and metabolism. Additional toxicokinetics studies would be useful in assessing differences in species sensitivity, and provide a better basis for extrapolation of animal data to human exposure risk.

Mitigation of Effects. Methods for the mitigation of acute effects of boron poisoning include prevention of absorption of boron from the gastrointestinal tract and standard procedures used to prevent convulsions, severe dehydration or shock (Stewart and McHugh 1990). Saline diuresis, exchange transfusions, peritoneal dialysis, or hemodialysis may be employed to enhance removal of absorbed boron from the body (Goldfrank et al. 1990; Stewart and McHugh 1990). No additional information was located concerning mitigation of effects of lower-level or longer-term exposure to boron. Further information on techniques to mitigate such effects would be useful in determining the safety and effectiveness of possible methods for treating boron-exposed populations in the vicinity of hazardous waste sites.

2.9.3 On-going Studies

The National Institute of Environmental Health Sciences (J. Williams, investigator) is conducting a study on the disposition of boric acid in selected target and nontarget tissues. The potential of boric acid to cause in vivo riboflavin deficiency as a mechanism of the testicular toxicity is being investigated, as are the direct effects of boric acid applied to sertoli or leydig cells in primary culture from naive rats (CRISP 1990).